Remarks

Reconsideration of this Application is respectfully requested.

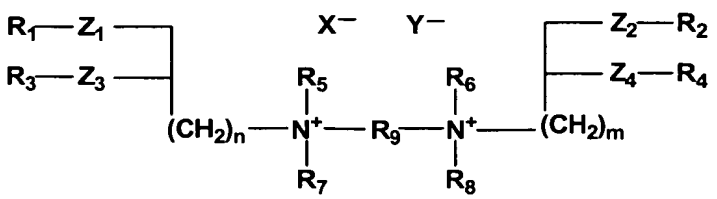
Upon entry of the foregoing amendments, claims 47-97 are pending in the application, with 47 and 83 being the independent claims. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicant respectfully requests that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Support for new claims 95-97 can be found in the examples at page 28, line 18, to page 30, line 22.

Description of the Invention

The present invention is directed to particular cationic compounds, compositions comprising said cationic compounds, methods of using said cationic compounds, and pharmaceutical kits comprising said cationic compounds. Specifically, the cationic compounds of the present invention are cationic dimers having the following formula:



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wherein R_1-R_9, Z_1-Z_4, n, m, X^- and Y^- are defined therein. The cationic dimers of the present invention are useful for, *inter alia*, enhancing the delivery of biologically active compounds to a cell. More particularly, R_9 is a linker moiety which is selected from a group of moieties as described in the present patent application.

Amendment to the Drawings

Substitute Figures 1A, 1B, 2, and 3 have been submitted herewith. Figures 1A and 1B have been amended to delete text which has been moved to the specification of the patent application. *See infra*. Applicant submits that no new matter has been added.

Amendment to the Specification

Applicant has amended the third full paragraph on page 6 (lines 14-18) of the specification. In the substitute paragraph, the chemical name of PentaEG-bis-DMRIE has been inserted. This text was originally located in Figure 1B.

Applicant has amended the last paragraph on page 6 (line 26), which continues to page 7 (line 4), of the specification. In the substitute paragraph, the chemical names of HB-DMRIE-Ox-Trp-γ- DMRIE and PEG34-bis-But-DMRIE-propylamide have been inserted. The molecular formula of HB-DMRIE-Ox-Trp-γ- DMRIE has been inserted. This text was originally located in Figure 1B.

Applicant has amended the second full paragraph on page 7 (lines 6-13) of the specification. In the substitute paragraph, the chemical names and molecular formulas of

SBDU-DMRIE, SBGU-DMRIE, and SHGU-DMRIE have been inserted. This text was originally located in Figure 1A.

Applicant has amended the third full paragraph on page 8 (lines 17-21) of the specification. In the substitute paragraph, the description of the figures has been modified to indicate that only the chemical structures are provided in the figures.

Applicant hereby requests correction of obvious, typographical errors. First, the molecular formula of HB-DMRIE-Ox-Trp-γ- DMRIE was incorrectly written as $C_{64}H_{160}Br_2N_5O_6$, in Figure 1B. Applicant has corrected the error, as shown in the replacement paragraph above. Support for the chemical formula can be found in the chemical structure shown in Figure 1B. Second, the chemical names of SBDU-DMRIE, SBGU-DMRIE, and SHGU-DMRIE were incorrectly written in Figure 1A. Applicant has corrected the error, as shown in the above amendment to the second full paragraph on page 7 (lines 6-13). Support for this amendment can be found at page 12, lines 22-30, and in the chemical structures of the compounds, as shown in Figure 1A.

Objection to the Claims

The Examiner has objected to claims 68-70, 74-78, 82, 84-86, 93, and 94 as depending from a rejected claim, namely claim 47. Applicant respectfully asserts that, based on the arguments presented *infra*, claim 47 is patentable. Therefore, claims 68-70, 74-78, 82, 84-86, 93, and 94 are in condition for allowance. Applicant submits that the Examiner's objection to claims 68-70, 74-78, 82, 84-86, 93, and 94 has been traversed. Reconsideration and withdrawal of the objection is respectfully requested.

Rejections under 35 U.S.C. § 112

The Examiner has rejected claims 79-81 under 35 U.S.C. § 112, second paragraph, as being indefinite. Specifically, the Examiner states that claims 79-81 recite "the encoded antigen" without antecedent basis. Applicant respectfully traverses the rejection.

Solely in order to further the prosecution of the present application, Applicant has amended claim 79 to depend from claim 77, as suggested by the Examiner. As amended, the term "the encoded antigen" of claim 79 has antecedent basis in the term "immunogen-encoding polynucleotide" of claim 77. Applicant respectfully notes that the amendment does not narrow the scope of claims 79-81.

In view of the above arguments and amendment, Applicant submits that the Examiner's rejection of claims 79-81 have been accommodated and respectfully requests reconsideration and withdrawal of the rejection of claims 79-81 under 35 U.S.C. § 112, second paragraph.

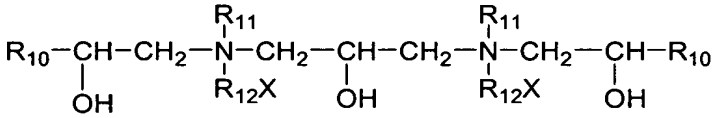
Rejections under 35 U.S.C. § 102

The Examiner has rejected claims 47-49 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 3,983,079 ("the '079 patent"). Specifically, the Examiner states that the '079 patent "teaches a composition according to the structure recited in instant claims 47 and 48, wherein R_9 is the substituted alkyl group CH_2-CHOH-CH_2." Applicant respectfully traverses the rejection.

The Examiner points to column 3, lines 60-65, of the '079 patent as supporting his conclusion that the '079 patent teaches a composition according to the present invention. The Examiner also cites column 13, lines 28-30, which discloses tetramethyl-di-(octoxy-β-

hydroxypropyl)-β-hydroxypropylene-diammonium chloride. Applicant respectfully submits that neither the cited genus of compounds nor the specific compounds disclosed in the '079 patent fall within the scope of Applicant's claimed invention.

The '079 patent discloses a broad genus of compounds that are useful in detergent compositions. (The '079 patent, col. 2, ll. 28-65). The specific examples to which the Examiner refers are described as follows.

> Specific examples of compounds having two quaternary ammonium groups, and two long aliphatic hydrocarbon radicals are represented by the formula:
>
> 
>
> wherein R_{10} is an alkyl radical containing from 6 to about 20, preferably 10 to 14, carbon atoms, and R_{11} and R_{12} are methyl, ethyl or hydroxyethyl, and the cation X^- is a chloride or bromide.

(*Id.*, col. 3, line 58, to col. 4, line 2.)

The present invention is distinguished from the above compounds of the '079 patent in that the prior art compounds require R_{10} to be an alkyl radical containing from about 6 to about 20 carbon atoms. The novel compounds of the present invention require hydroxy, ether, or ester substituents at the same position as R_{10}; *i.e.*, R_1-Z_1- or R_2-Z_2- is a hydroxy, ether, or ester group.

The '079 patent also appears to disclose several specific compounds, all of which do not fall within the scope of Applicant's claimed invention. For example, the Examiner cites tetramethyl-di-(octoxy-β-hydroxypropyl)-β-hydroxypropylene-diammonium chloride, at col. 13, lines 28-30. Additional species which appear to be disclosed are tetramethyl-di-(β-hydroxydodecyl)-β-hydroxypropylene-diammonium bromide, tetramethyl-di-(β-

hydroxytetradecyl)-β-hydroxypropylene-diammonium chloride, and tetraethyl-di-(dodecyloxy-β-hydroxypropyl)-β-hydroxypropylene-diammonium chloride. (*See id.*, col. 4, ll. 2-9).

None of the aforementioned species is encompassed by the presently claimed invention. The novel compounds of the claimed invention require that "R_3 and R_4 are the same or different and are C_1 to C_{24} alkyl or C_1 to C_{10} alkenyl." None of the disclosed species in the '079 patent meets this limitation. All of the disclosed species contain a hydroxyl group at the positions which correspond to R_3 and R_4 of Applicant's compounds.

Applicant respectfully submits that the '079 patent does not teach a compound according to the present invention and, therefore, the present invention is not anticipated by the '079 patent. Furthermore, the '079 patent does not provide any teaching or suggestion to make a compound of the present invention.

In view of the above arguments, Applicant asserts that claims 47-49 are not anticipated under 35 U.S.C. § 102(b) by the '079 patent and respectfully requests reconsideration and withdrawal of the rejection of claims 47-49 under 35 U.S.C. § 102(b).

Rejections under 35 U.S.C. § 103

The Examiner has rejected claim 83 under 35 U.S.C. § 103(a) as being obvious over the '079 patent. According to the Examiner, the '079 patent teaches a composition according to instant claim 83 and it would have been obvious to one of skill in the art to store said composition in a container. Applicant respectfully traverses the rejection.

As explained above, the '079 patent does not teach a compound having the structure of the present invention. Furthermore, in view of the teaching of the '079 patent, it would

not have been obvious to one of ordinary skill in the art to make the novel compounds of the present invention. The prior art does not suggest changing the hydroxyl groups of the prior art compounds to the alkoxy or alkenoxy groups of R_3 and R_4 of the claimed invention. Accordingly, it would not have been obvious to make the kit according instant claim 83. Therefore, the claimed invention is nonobvious and patentable.

In view of the above arguments, Applicant asserts that claim 83 is not obvious under 35 U.S.C. § 103(a) in view of the '079 patent and respectfully requests reconsideration and withdrawal of the rejection of claim 83 under 35 U.S.C. § 103(a).

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Matthew J. Dowd

Matthew J. Dowd
Agent for Applicant
Registration No. 47,534

Date: April 8, 2003

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

Version with markings to show changes made

In the Specification

Please substitute the third full paragraph on page 6 (lines 14-18) with the following paragraph:

--In certain preferred embodiments, where the cationic lipid compound has a structure according to formula (I), the linker is optionally substituted C_1 to C_{10} alkyl or alkyloxy, or optionally substituted C_1 to C_{10} alkenyl or alkenyloxy. In a particularly preferred embodiment, the cationic lipid compound is PentaEG-bis-DMRIE, the chemical structure of which is shown in Figure 1B. The chemical name of PentaEG-bis-DMRIE is penta(ethylene glycol), α, ω-bis-(±)-N-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-1-propanaminium bromide ether.--

Please substitute the last paragraph on page 6 (line 26), which continues to page 7 (line 4), with the following paragraph:

In certain other preferred embodiments, where the cationic lipid compound has a structure according to formula (I) described below, the linker has DNA and/or cell receptor binding affinity. Such linkers may enhance the effectiveness of the lipid in interacting with nucleotides and/or cell membranes. Examples of moieties having such binding affinity include, for example, amino acids, peptides, saccharides, polypeptides,

polysaccharides, proteins, polyamines, peptidomimetic moieties and histories. Specific examples of polyamines having such binding affinity include spermine, spermidine, and derivatives thereof. In particularly preferred embodiments incorporating a peptide moiety, the cationic lipid is HB-DMRIE-Ox-Trp-γ-DMRIE or PEG34-bis-But-DMRIE-propylamide, the chemical structures of which are shown in Figure 1B. The chemical name of HB-DMRIE-Ox-Trp-γ-DMRIE is (±)-N-[4-(N'-(3'-tryptophanylaminopropyl))-N',N'-dimethyl-2',3'-bis(tetradecyloxy)-1'-propanaminiumyl]-N,N-dimethyl-2,3-bis(tetradecyloxy)-1-propanaminium bromide. The molecular formula of HB-DMRIE-Ox-Trp-γ-DMRIE is $C_{84}H_{161}Br_2N_5O_6$. The chemical name of PEG34-bis-But-DMRIE-propylamide is poly(ethylene glycol)-34 bis-[(±)-N-(N'-propylbutyramido)-N,N-dimethyl-2,3-bis(tetradecyloxy)-1-propanaminium bromide].

Please substitute the second full paragraph on page 7 (lines 6-13) with the following paragraph.

In yet other preferred embodiments, where the cationic lipid compound has a structure according to formula (II), the linker bridging the quaternary ammonium headgroups includes a bis-ureyl linkage. In certain embodiments, the cationic lipid compound is a dimer, wherein the hydrophobic lipid tails, represented by groups R_1 to R_4, are identical. In particularly preferred embodiments, the cationic lipid compound is SBDU-DMRIE, SBGU-DMRIE or SHGU-DMRIE, the chemical structures of which are provided in Figure 1A. Another common name of SBDU-DMRIE is butane bis-DU-DMRIE. The chemical name of SBDU-DMRIE is 1,4-bis-(N'-butyl-(4-(N,N-dimethyl-

2,3-bis(tetradecyloxy)-1-propanaminium))-ureyl-butane. The molecular formula is $C_{80}H_{166}O_6N_6$. Another common name of SHGU-DMRIE is hexane bis-1,6-GU-DMRIE. The chemical name of SHGU-DMRIE is 1,4-bis-(N'-propyl-(4-(N,N-dimethyl-2,3-bis(tetradecyloxy)-1-propanaminium))-ureyl-hexane. The molecular formula is $C_{80}H_{166}O_6N_6$. Another common name of SBGU-DMRIE is butane bis-GU-DMRIE. The chemical name of SBGU-DMRIE is 1,4-bis-(N'-propyl-(4-(N,N-dimethyl-2,3-bis(tetradecyloxy)-1-propanaminium))-ureyl-butane. The molecular formula is $C_{80}H_{166}O_6N_6$. These compositions may also optionally include one or more co-lipids.

Please substitute the third full paragraph on page 8 (lines 17-21) with the following paragraph.

Figures 1A and 1B provide the [various names, as well as the molecular formula and] chemical structures[,] for six preferred cationic lipid compounds for use in the compositions of the present inventions: SBDU-DMRIE; SBGU-DMRIE; HB-DMRIE-Ox-Trp-γ-DMRIE; PentaEG-bis-DMRIE; and PEG34-bis-But-DMRIE-propylamide.

In the Claims

79. (Once Amended) A method for inducing an immune response in a vertebrate, said method comprising administering to the vertebrate an immunogenic composition of claim 77 [76] in an amount sufficient to generate an immune response to the encoded immunogen.

Claims 95-97 are new.

In the Drawings

Substitute Figures 1A, 1B, 2, and 3 replace original Figures 1A, 1B, 2, and 3 respectively.